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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/945,459	12/09/1997	FUSAO MAKISHIMA	146.1275	2741

6449 7590 05/17/2005

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/945,459	MAKISHIMA ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 02/07/2005 has been entered. Claims 49-66 are pending and being examined.

Claim Rejections - 35 USC § 103

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13).

Applicants argue that Celeste was not able to prove bone/cartilage-inducing activity for mature MP52 and that there is even less indication for short fragments from which a reduced interaction with ECM is to be expected. Applicant's arguments have been fully considered but they are not persuasive. A chemical composition and its properties are inseparable. Therefore, the properties applicant discloses and/or claims, i.e. "has cartilage and/or bone morphogenetic activity", are necessarily present in the protein taught by the cited prior art. Nor are these properties, i.e. "cartilage and/or bone morphogenetic activity," unexpected because the present specification at page 2, lines 1-3, discloses that the bone morphogenetic activity of MP52 has been reported. Furthermore, Hotten (A, Paper No. 37, mailed 05/27/2003) discloses that in both experimental animals considerable formation of cartilage and bone was detected in the implants containing [2 to 4 μg] MP52. See column 14, lines 60-64. This response was confirmed in two different assays. See column 16, full paragraph 1, "These results also confirm that MP52 can induce endochondral bone formation." The shortened form of MP52 taught by the cited

references, i.e., MP52 with a Pro at the N-terminus, is not missing any of the basic amino acid residues alleged by Applicants (page 8 of the response filed 02/17/2004) to be important for interaction with ECM. Furthermore, Applicants have not presented any experimental data showing that the activity of MP52 with a Pro at the N-terminus is any different from MP52 with an Ala-Pro at the N-terminus. The examiner concludes that Applicants' argument is mere argument. Arguments of counsel cannot take the place of evidence in the record.

Applicants argue that only Ala-Pro-MP52 is naturally occurring, and that Pro-MP52 is not a natural product and would be inappropriate for the pharmaceutical industry according to Georgiou. Applicant's arguments have been fully considered but they are not persuasive. The examiner did not state that Ala-Pro-MP52 and Pro-MP52 are natural products. The examiner stated "Met-Ala-Pro-MP52 is not identical to the natural product, Ala-Pro-MP52 and Pro-MP52 are identical to the natural product." The examiner relies upon Georgiou for teaching removal of the N-terminal Met. When faced with a choice between either a composition comprising Met-Ala-Pro-MP52, Ala-Pro-MP52, and Pro-MP52 or a composition comprising Ala-Pro-MP52 and Pro-MP52, the composition comprising Ala-Pro-MP52, and Pro-MP52 is the obvious choice because Met-Ala-Pro-MP52 is not identical to the natural product. One of ordinary skill in the art would be further motivated to obtain Pro-MP52 because it is generally considered desirable for clinical use to obtain a homogeneous material, i.e. a protein having essentially the same N-terminal sequence from molecule to molecule (Thompson, paragraph bridging columns 1-2).

Applicants argue that Ben-Bassat's method has disadvantages and that it cannot be assumed that 100% cleavage of methionine will be obtained simply by increasing the amount of enzymes because Ben-Bassat teaches that some N-terminal methionine remained despite the

disadvantageous use of increased amounts of enzyme. Applicant's arguments have been fully considered but they are not persuasive. The process limitations in claim 49 do not limit the claimed product and do not distinguish the claimed product from Pro-MP52 obtained by a different process, such as Pro-MP52 obtained by using one or more aminopeptidases. It is noted that a composition comprising major amounts of one or more aminopeptidases and isolated Pro-MP52 is encompassed by claim 49. Although Ben-Bassat teaches that a small fraction of the proteins retained their terminal methionines after being exposed to MAP in vivo, one of ordinary skill in the art would still be motivated to obtain Ala-Pro-MP52 and Pro-MP52 because Met-Ala-Pro-MP52 is not identical to the natural product. The examiner does not agree that Ben-Bassat used "increased amounts of enzyme," as asserted by Applicants, because Ben-Bassat did not vary the amount of enzyme. Ben-Bassat also states that "No kinetic studies were conducted to investigate the optimal conditions and the time courses of these reactions" (page 752, right column, full paragraph 4).

Applicants argue that Tonouchi means an additional treatment step, that contamination can be expected, that aminopeptidase P would not cleave Met-Ala-Pro-MP52. Applicant's arguments have been fully considered but they are not persuasive. Claim 49 is drafted in the product-by-process format. The process limitations in claim 49 do not limit the claimed product and do not distinguish the claimed product from Pro-MP52 obtained by a different process, such as Pro-MP52 obtained by using one or more aminopeptidases. It is noted that a composition comprising major amounts of one or more aminopeptidases and isolated Pro-MP52 is encompassed by claim 49. Furthermore, one of ordinary skill in the art would be motivated to obtain Ala-Pro-MP52 and Pro-MP52 because Met-Ala-Pro-MP52 is not identical to the natural

product. Therefore, Ala-Pro-MP52 is the product that would be used in Tonouchi's process to obtain Pro-MP52. One of ordinary skill in the art would be motivated to obtain Pro-MP52 because it is generally considered desirable for clinical use to obtain a homogeneous material, i.e., a protein having essentially the same N-terminal sequence from molecule to molecule.

Applicants argue that the process of the present application unexpectedly results in the expression of MP52 alone, i.e., completely without, Met-Ala-Pro-MP52 or Ala-Pro -MP52, at an unexpectedly high expression rate with an efficient cleavage of the methionine. Applicant's arguments have been fully considered but they are not persuasive. Claim 49 is drafted in the product-by-process format. The process limitations in claim 49 are not viewed as positively limiting the claimed product and do not distinguish the claimed product from Pro-MP52 obtained by a different process, such as Pro-MP52 obtained by using one or more aminopeptidases.

Applicants discussion of Devlin and Looman (pages 8-9 of Applicants' response; it is noted that the Looman reference has not been made of record) is acknowledged. However, the present rejection does not rely upon Devlin and Applicants' arguments regarding Devlin and Looman are only pertinent to the expression of Met-Pro-MP52, whereas the present rejection pertains to the expression of Met-Ala-Pro-MP52.

Applicants argue that Met-Ala-Pro-MP52 and Ala-Pro-MP52 are not expressed in the present invention, that it is not necessary to use aminopeptidase P when using the present invention, and that claim 49 has been amended to clarify that Met-Ala-Pro-MP52 and Ala-Pro-MP52 are not expressed. Claim 49 is drafted in the product-by-process format. The process limitations in claim 49 are not viewed as positively limiting the claimed product and do not

distinguish the claimed product from Pro-MP52 obtained by using a different process, such as Pro-MP52 obtained by using one or more aminopeptidases.

Claims 49, 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13) as applied to claim 49 above and further in view of Hotten (2, cited by Applicants) and Cerletti (N, Paper No. 10).

Applicants argue that Met-Ala-Pro-MP52 and Ala-Pro-MP52 are not expressed in the present invention, that it is not necessary to use aminopeptidase P when using the present invention, and that claim 49 has been amended to clarify that Met-Ala-Pro-MP52 and Ala-Pro-MP52 are not expressed. Applicant's arguments have been fully considered but they are not persuasive. Claim 49 is drafted in the product-by-process format. The process limitations in claim 49 are not viewed as positively limiting the claimed product and do not distinguish the claimed product from Pro-MP52 obtained by using a different process, such as Pro-MP52 obtained by using one or more aminopeptidases.

Claims 49-60, 63, 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13) as applied to claim 49 above and further in view of Hotten (2, cited

by Applicants) and Cerletti (N, Paper No. 10) as applied to claims 49, 50 above and further in view of Neidhardt (1, cited by Applicants).

Applicants argue that Neidhardt does not cure the deficiencies of the other references regarding the expression of Met-Ala-Pro-MP52 and Ala-Pro-MP52, and that claim 49 has been amended to clarify that Met-Ala-Pro-MP52 and Ala-Pro-MP52 are not expressed. Applicant's arguments regarding the deficiencies of the other references have been fully considered but they are not persuasive for the reasons discussed above.

Claims 49-51, 64, 65 and claims 52-60, 63, 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13) as applied to claim 49 above and further in view of Hotten (2, cited by Applicants) and Cerletti (N, Paper No. 10) as applied to claims 49, 50 above and further in view of Neidhardt (1, cited by Applicants) as applied to claim 51 above and further in view of Hotten (A, Paper No. 37) and Chen (U. S. Patent No. 5707962).

Applicants argue that Chen does not cure the deficiencies of the other references regarding the expression of Met-Ala-Pro-MP52 and Ala-Pro-MP52, and that claim 49 has been amended to clarify that Met-Ala-Pro-MP52 and Ala-Pro-MP52 are not expressed. Applicant's arguments regarding the deficiencies of the other references have been fully considered but they are not persuasive for the reasons discussed above.

Applicants argue that none of these references suggest that it is possible to express proteins according to SEQ ID NO: 1 without expressing Met-Ala-Pro-MP52 and Ala-Pro-MP52,

and that additional steps are required when using the prior art processes. Applicant's arguments regarding the deficiencies of the other references have been fully considered but they are not persuasive for the reasons discussed above. Furthermore, claim 49 is drafted in the product-by-process format. The process limitations in claim 49 are not viewed as positively limiting the claimed product and do not distinguish the claimed product from Pro-MP52 obtained by using a different process, such as Pro-MP52 obtained by using one or more aminopeptidases.

Claims 49-51, 61, 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13) as applied to claim 49 above and further in view of Hotten (2, cited by Applicants) and Cerletti (N, Paper No. 10) as applied to claims 49, 50 above and further in view of Neidhardt (1, cited by Applicants) as applied to claim 51 above and further in view of Ron (U. S. Patent No. 5,171,579) and Avis (Avis, K.E. "Parenteral Preparations", Chapter 84, in, Remington's Pharmaceutical Sciences, 18th edition (June 1990), Mack Pub. Co., Easton, Pennsylvania).

Applicants argue that Ron's pharmaceutical composition is implanted and not injected, that clotted blood is not injectable, that Avis does not indicate that the presently claimed protein can be prepared and lyophilized, and that Ron and Avis do not cure the deficiencies in the other references regarding the expression of Met-Ala-Pro-MP52 and Ala-Pro-MP52, and that claim 49 has been amended to clarify that Met-Ala-Pro-MP52 and Ala-Pro-MP52 are not expressed. Applicant's arguments have been fully considered but they are not persuasive. In response to

applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The present specification discloses that injectable preparations can be formulated in the form of injectable powders. The powders can be prepared by adding one or more of suitable water-soluble excipients such as mannitol, sucrose, lactose, maltose, glucose, fructose and the like, to an active ingredient, dissolving the mixture in water, dividing it into vials or ampoules followed by lyophilizing and hermetically sealing. See page 7, full paragraph 2. Accordingly, a lyophilized preparation comprising MP52 and a pharmaceutically acceptable carrier is a pharmaceutical composition comprising MP52 wherein said pharmaceutical carrier is suitable for an injectable powder. The examiner relies on Ron for teaching the lyophilization of an osteogenic protein and on Avis for the teachings regarding lyophilization. Applicants' arguments do not speak to the obviousness of lyophilizing pharmaceutical preparations of MP52. Applicants' argument that Avis does not indicate that the presently claimed protein can be prepared and lyophilized is conclusory and unsupported. Applicant's arguments regarding the deficiencies of the other references have been fully considered but they are not persuasive for the reasons discussed above. Furthermore, claim 49 is drafted in the product-by-process format. The process limitations in claim 49 are not viewed as positively limiting the claimed product and do not distinguish the claimed product from Pro-MP52 obtained by using a different process, such as Pro-MP52 obtained by using one or more aminopeptidases.

Claims 49-51, 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over [{Celeste (A, Paper No. 10), Ben-Bassat (W, Paper No. 10), and Hirel (U, Paper No. 20)} in view of Georgiou (X, Paper No. 13)] and further in view of Thompson (A, Paper No. 27) and Tonouchi (Y, Paper No. 13) as applied to claim 49 above and further in view of Hotten (2, cited by Applicants) and Cerletti (N, Paper No. 10) as applied to claims 49, 50 above and further in view of Neidhardt (1, cited by Applicants) as applied to claim 51 above and further in view of Oppermann (U. S. Patent No. 5354557).

Applicants argue that Oppermann aims at producing an implant made of osteogenic protein and a matrix, which are not suitable for injection, that Oppermann does not suggest that osteogenic proteins are active in saline alone nor does he suggest that osteogenic proteins can be used systemically, and that Oppermann does not cure the deficiencies in the other references regarding the expression of Met-Ala-Pro-MP52 and Ala-Pro-MP52, and that claim 49 has been amended to clarify that Met-Ala-Pro-MP52 and Ala-Pro-MP52 are not expressed. Applicant's arguments have been fully considered but they are not persuasive. The claims only require that the pharmaceutical carrier be suitable for injection. Oppermann discloses osteogenic protein preparations in physiological saline. Regardless of any subsequent use of or addition to osteogenic protein preparations in physiological saline, physiological saline is a "pharmaceutical carrier" "suitable for injection." Applicant's arguments regarding the deficiencies of the other references have been fully considered but they are not persuasive for the reasons discussed above. Furthermore, claim 49 is drafted in the product-by-process format. The process limitations in claim 49 are not viewed as positively limiting the claimed product and do not

distinguish the claimed product from Pro-MP52 obtained by using a different process, such as Pro-MP52 obtained by using one or more aminopeptidases.

Double Patenting

Claims 49-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 10365231. Applicants' request to hold this rejection in abeyance is acknowledged. However, there are no provisions for holding a rejection in abeyance.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH

FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
MAY 12, 2005